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Nutritional and metabolic changes during drug therapy

ICU patients: how to deal with medication interference to nutritional treatment?

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ICU Patients: how to deal with medication interference to nutritional treatment?

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Clinical Pharmacology
ICU patients
Drug dosing
Drug interactions
Drug-nutrient interactions
EN-drug interactions
TPN-drug interactions
Intensive Care Unit

- An intensive care unit is a specialised section of a hospital that provides comprehensive and continuous care for critically ill patients and who can benefit from treatment.

- Patients in ICU are often given 10 or more drugs simultaneously. As the number of drugs, severity of illness, and patient age increase, so does the risk of an adverse drug reaction.
Drug Dosing

- Bioavailability
- Volume of distribution
- Clearance
- Half life
Drug interactions can occur via several mechanisms:

- Formulation
- Absorption
- Distribution
- Metabolism
- Elimination
- Drug action site
Drug-drug inter (met)

Some important preventable drug interaction are due to their effects on drug metabolising enzymes, resulting in either inhibition of the enzyme or induction of the enzyme.

Metabolic interaction mechanisms are also important in drug-nutrient interactions.
CYP 450

The major group of the enzymes in the liver that metabolize drugs can be isolated in a subcellular fraction termed the micromosomes. The largest and most important of these enzymes are the cytochrome p450 family of enzymes.

CYP450 were named by molecular biologist and protein chemist. The enzyme named according to families that are defined by the similarity of their amino acid sequence.
Cytochrome P450 (CYP450)

- Superfamily: CYP
  - Family: 1-4
    - Subfamily: A-E
      - Isozyme: 1-25
  - CYP3A4

Pharmacokinetics
enzymes

Phase I
- CYP1B1
- CYP2A6*
- CYP2B6
- CYP2C8/9*
- CYP2C19*
- CYP2D6*
- CYP2E1
- CYP3A4/5

Phase II
- Epoxide hydrolase
- DPYD*
- Others
- Esterases
- TPMT*
- NATs*
- GSTs*
- STs*
- UGTs*
CYP 450

- Mutations
- Metabolizing activity
- Polimorphism
DRUG INTERACTIONS

- Charts
- Websites
- Databases
Drug-nutrient Interactions

Early studies focused mostly on the potential changes in drug absorption caused by concurrent food or meal intake. Clinicians therefore have instructed patients not to take interfering nutrient with drugs. The term drug-nutrient interaction can be defined as an alteration of kinetics or dynamics of a drug or a nutritional element.
Nutritional Status in ICU

Nutritional status is now recognised to be an important part of medical care and nutritional support can be provided enterally or parenterally in various patient groups in ICU.

The use of either the enteral or parenteral route provides pharmaceutical challenges in the delivery of medication usually delivered by the oral route.

Factors such as concomittant disease states (renal failure, hepatic failure, short bowel syndrome) obesity or malnutrition can alter the pharmacokinetiks of a medicine.
Pharmacologist role

- Pharmacologist need to be more actively involved in the medical treatment of these patients.
- Better communication was required between primary and secondary care.
Administration of medicine

- The type of tube
- Placement site
- Site of drug absorption.
Mechanism of interactions

- Ex vivo biopharmaceutical inactivations
- Interactions affecting absorption phase
- Interactions affecting systemic/physiologic dispositions
- Interactions affecting elimination/clearance

Gordon Sacks. Drug-nutrient Considerations in patients receiving parenteral and enteral nutrition. Practical Gastroenterology, July 2004
EN Formulations

- The preferred and easiest way to administer drugs through a tube is as a liquid preparation.
- The amount of water used should be documented on the appropriate fluid balance sheets.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Use supposituars</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Liquid has different bioavailability from tablets so dose adjustment may be necessary</td>
</tr>
<tr>
<td>Lithium</td>
<td>Total daily dose needs to be given in more frequent divided doses</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Total daily dose may need to be given more frequently. For controlled release formulation 400 mg levodopa is equivalent to 300-400 mg levodopa ordinary preparations.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90 mg phenytoin liquid is approximately equivalent to 100 mg capsules.</td>
</tr>
<tr>
<td>Sodium fusidate</td>
<td>500 mg sodium fusidate tablets are approximately equivalent to 750 mg fusidic acid suspension</td>
</tr>
<tr>
<td>All ‘retard’ formulations</td>
<td>Total daily dose may need to be given more frequently</td>
</tr>
</tbody>
</table>
EN: Drug Formulations

- Liquid preparations
- Soluble and dispersible tablets
- Tablets and capsules
- Crushed tablets
Main Principles to avoid drug-nutrient interactions

- **Timing of drug administration**
  - Maximize absorption of drugs
  - Minimise drug-feed interactions

- **Avoiding tube blockage**
  - Using appropriate prep
  - Avoiding drug interactions with feeds
  - Avoiding the use of acidic liquids
  - Consideration of feeding tube size
### Examples of drug interactions with enteral feeds

<table>
<thead>
<tr>
<th>Medication</th>
<th>Type of interactions</th>
<th>Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Absorption decreased 25%, chelation with ions in tap water</td>
<td>Stop enteral feeding for one hour and two hours after dose</td>
</tr>
<tr>
<td>Hidralasine</td>
<td>Decreased absorption and concentration</td>
<td>Monitor changes in blood pressure</td>
</tr>
<tr>
<td>Penicilline V</td>
<td>Unpredictable absorption</td>
<td>Stop enteral feed for one hour before and two hours after</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Binds to protein in the feed</td>
<td>Use alternatives, ranitidine</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Metabolism and absorption decreased</td>
<td>Stop feed for one hour before and two hours after and monitor levels</td>
</tr>
<tr>
<td>Warfarin</td>
<td>May interact with vitamin K content of feed</td>
<td>Monitor INR close or use parenteral heparin when critical</td>
</tr>
</tbody>
</table>
Antacids

Aluminium-containing antacids

Oesophageal plug in patients given aluminium/magnesium hydroxide while receiving high protein enteral feeds has been described. Hypophosphatemia.

Tomlin ME et al Aluminium and nasogastric feeds. PharmJ 1996;256:40

Anticonvulsants

- Phenytoin
  - Low albumin
  - Interacting other drugs
- Carbamazepine
  - Liquids
  - Suppositories

Krueger KA. Effect of two administrations of an enteral nutrient formula on phenytoin bioavailability. Epilepsia 1987;28:706-12

Minimising interactions between liquid phenytoin and enteral feeds

- Give as a single dose
- Stop enteral feed two hours before and after administration of phenytoin or suspend feed between 10 pm and 6 am and give phenytoin as a single daily dose at midnight
- Dilute phenytoin suspension with at least equal parts
- Flush enteral tube with plenty of water before and after administration
Warfarin

The vitamin K content of feeds

A three-hour gap between stopping the feed and administering warfarin


20.10.2006
Theophylline

- Differences in pharmacokinetics related to the protein and carbohydrate contents of diet.
- The mechanism may be related to changes in metabolism as a result of protein and carbohydrate effects on stimulating and inhibiting cytochrome P450.
- Stop feeding before and after administration and monitor plasma levels of the drug.
Quinolone antibiotics

- Lower plasma concentrations
- The formation of insoluble chelates with divalent ions (calcium, magnesium etc)

Mimoz et al. Pharmacokinetics and absolute bioavailability of ciprofloxacin administered through a nasogastric tube with continuous enteral feeding to critically ill patients, Intensive care Med 1998;24:1047-51
TOTAL PARENTERAL NUTRITION

- It is employed in patients where an adequate dietary intake cannot be maintained via GI tract.
- If alternative routes are suitable parenteral administration of drugs may be required.
- IV drug-drug incompatibilities have been described, less is known about drug-parenteral feed incompatibilities.

Factors which affect drug and TPN stability:

- Composition of TPN regimen
- Contact time between drug and TPN solution
- Brand and concentration of drug added
- Exposure of admixture to temperature and light.
TPN: Routes of Drug administration

- The multi-lumen catheter
- Y-site connection
- Addition of drugs to parenteral feeds
- Drug-induced effects on electrolytes and cumulative fluid volumes
Warfarin resistance was noted in a patient receiving a TPN solution containing intralipid.

Lipid emulsions may increase the production of clotting factors supply sufficient vitamin K to increase the production of clotting factors.

Lutomski et al. Warfarin resistance associated with intravenous lipid administration. JPEN 1987;11:316-8

Theophylline

One case report of an elderly woman treated with IV aminophylline described a marked fall in theophylline levels when the amino acid concentration of her TPN solution was increased.

Ziegenbein RC. Theophylline clearance increase from increased amino-acid in CPN regimen. DICP 1987;21:220-1
A single case report of a 40 year old man described decrease total phenytoin levels during the administration of TPN, which subsequently increased to pre-TPN levels following discontinuation of TPN.

Conclusion

Drug interaction with TPN solutions are not reported in the literature as commonly as those relating to drug interactions with enteral feeding solutions.
Thank you for your attention